EXHIBIT 17

Resistive-Polymer Versus Forced-Air Warming: Comparable Efficacy in Orthopedic Patients

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BACKGROUND: Several adverse consequences are caused by mild perioperative hypothermia. Maintaining normothermia with patient warming systems, today mostly with forced air (FA), has thus become a standard procedure during anesthesia. Recently, a polymer-based resistive patient warming system was developed. We compared the efficacy of a widely distributed FA system with the resistive-polymer (RP) system in a prospective, randomized clinical study.
METHODS: Eighty patients scheduled for orthopedic surgery were randomized to either FA warming (Bair Hugger warming blanket #522 and blower #750, Arizant, Eden Prairie, MN) or RP warming (Hot Dog Multi-Position Blanket and Hot Dog controller, Augustine Biomedical, Eden Prairie, MN). Core temperature, skin temperature (head, upper and lower arm, chest, abdomen, back, thigh, and calf), and room temperature (general and near the patient) were recorded continuously.
RESULTS: After an initial decrease, core temperatures increased in both groups at comparable rates (FA: 0.33°C/h ± 0.34°C/h; RP: 0.29°C/h ± 0.35°C/h; $P = 0.6$). There was also no difference in the course of mean skin and mean body (core) temperature. FA warming increased the environment close to the patient (the workplace of anesthesiologists and surgeons) more than RP warming (24.4°C ± 5.2°C for FA vs 22.6 °C ± 1.9°C for RP at 30 minutes; $P_{AUC} < 0.01$).
CONCLUSION: RP warming performed as efficiently as FA warming in patients undergoing orthopedic surgery. (Anesth Analg 2010;110:834–8)

Perioperative hypothermia is a common problem challenging the anesthesiologist. It is caused by the inhibition of thermoregulation induced by anesthesia, redistribution of body heat from the core to the periphery, and the exposure of the patient's skin and tissues to a cold environment in the operating room (OR).[1] Even mild hypothermia triples the incidence of postoperative wound infection and increases the hospital length of stay by 20%,[2] increases blood loss and blood transfusion requirements,[3] and increases the incidence of cardiovascular complications[4] and the thermal discomfort of patients.[5] Consequently, intraoperative active warming has become a standard procedure during general anesthesia. Forced-air (FA) warming, the most common approach, is relatively inexpensive, safe, easily performed, and has proven to be highly effective.[6–9]

Recently, a new warming system (Hot Dog, Augustine Biomedical, Eden Prairie, MN) was introduced that uses a different, conductive warming technology: an electric current heats a resistive-polymer (RP) blanket. This system might have some advantages compared with an FA warming system: blankets are reusable, there is no air flow and thus warming can be initiated immediately after induction of anesthesia without waiting for surgical draping to be completed, and its operation is silent. However, the principle of electric blanket warming is based primarily on conductive warming and therefore requires direct skin contact to work effectively. In contrast, FA systems work with redundant amounts of warm air, which also flow around large areas of the patient's skin not covered by the actual blanket; thus, a close contact between the FA blanket and the patient's skin is not required. This difference in the mechanisms of action partly explains the heterogeneous results of previous studies comparing resistive versus FA warming devices. Some authors have shown comparable warming efficacy of these 2 technologies.[10–13] Other authors have found the efficacy of resistive warming blankets to be inferior.[14,15] In these studies, carbon-fiber systems were primarily evaluated.

Recently, Kimberger et al.[16] published a crossover study comparing the Hot Dog RP warming system with a FA device and showed comparable heat transfer and rewarming rates in volunteers. In this study, we compared the Hot Dog RP warming system device with an FA warming system (Bair Hugger, Arizant, MN) in a randomized, controlled manner in surgical patients.

METHODS

With approval of the IRB of the Medical University of Vienna and written informed consent obtained on the day before surgery, we studied 80 patients undergoing elective orthopedic surgery with general or combined general-regional anesthesia. Before patient enrollment, this study was registered at www.clinicaltrials.gov under number NCT00772460. The only exclusion criterion was severe peripheral artery disease in the warmed extremity because FA patient warming is routinely used for all patients during these procedures.

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Accepted for publication November 8, 2009.

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DOI: 10.1213/ANE.0b013e3181cb3f5f

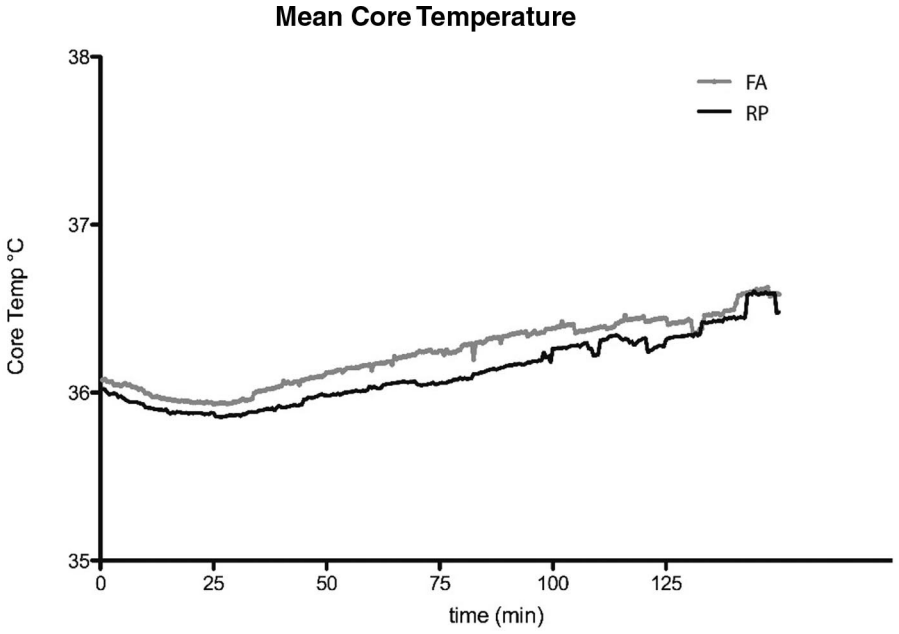

Figure 1. Mean core temperature (0 minute represents induction of anesthesia). Gray: forced air (FA) ($n = 40$); black: resistive polymer (RP) ($n = 40$).

Before induction of anesthesia, patients were randomly assigned, using a computer-generated randomization sequence in which the group assignment was kept in sequentially numbered, opaque envelopes, to 1 of 2 treatments: (1) FA warming (FA group) with a Bair Hugger upper body warming cover (model #522), connected to a model #750 warming unit set to "high" (43°C); or (2) RP warming (RP group) with 2 Hot Dog warming blankets (model: Multi-Position Blanket) and the Hot Dog controller unit set to "high" (43°C).

As recommended by the manufacturer, we used 2 Hot Dog Multi-Position Blankets, each approximately half the size of a typical upper body FA blanket. For upper body warming, straps connected the 2 Hot Dog blankets, resulting in 1 normal-size upper body blanket. Anesthetic, hemodynamic, and fluid management were at the discretion of the attending anesthesiologist. General anesthesia was provided with inhaled sevoflurane in oxygen and IV fentanyl as per departmental routine. Combined regional-general anesthesia consisted of general anesthesia in combination with femoral nerve block, and in all cases of regional anesthesia, spinal anesthesia was performed.

Measurements

Before induction of anesthesia, skin temperature probes (Mon-a-therm, Mallinckrodt Anesthesiology Products, St. Louis, MO) were attached to the patient's head, upper and lower arm, chest, abdomen, back, thigh, and calf. Mean body temperature was calculated using the Burton formula[17]:

$$\text{Mean body temperature} = 0.64 \times T_{\text{core}} + 0.36 \times T_{\text{skin}}$$

Mean skin temperature was calculated using a simplified formula based on body surface area:

$$0.06 \times T_{\text{head}} + 0.09 \times T_{\text{arm}} + 0.06 \times T_{\text{forearm}} + 0.19 \times T_{\text{back}} + 0.095 \times T_{\text{chest}} + 0.095 \times T_{\text{abdomen}} + 0.19 \times T_{\text{thigh}} + 0.115 \times T_{\text{calf}}$$

The core warming rate (°C/h) was calculated from a starting point 30 minutes after induction of anesthesia to the end of surgery, because the typical initial core temperature decrease reaches its maximum at this time (because of blood redistribution), and rewarming starts (Fig. 1).

After induction of anesthesia, a temperature probe (Smiths-Medical, London, UK) was inserted into the distal esophagus (in patients receiving general or combined anesthesia) or into the urinary bladder (in patients receiving regional anesthesia) to measure core body temperature; subsequently, warming with the randomized warming device was started. All temperature measurements were recorded every 5 minutes until the end of surgery. Additionally, we recorded demographic and morphometric variables (gender, age, and body mass index), the duration of surgery, type of anesthesia, IV infusions and blood loss, vasopressor therapy, and environmental temperature close to the patient (approximately 1 m distance) and in the OR. Thirty minutes after arrival in the postoperative care unit, the patient's individual thermal comfort was evaluated with a visual analog scale (VAS) (0 = extreme cold, 100 = extreme heat, and 50 = thermoneutrality). The necessity of postoperative warming was recorded, using the threshold for postoperative active warming of our institution (core temperature <35°C at the time of planned tracheal extubation).

Statistical Analysis

To calculate sample size, a power analysis for equivalence (unpaired test) was performed. Lower and upper equivalence bounds were ±0.5°C core temperature, with an SD of 0.6°C calculated from previous data. A total sample size of 80 patients was estimated to achieve a power of 90% to detect equivalence within the specified equivalence bounds. For the analysis of core and mean body temperature, we calculated the area under the temperature curves (AUCs), normalized for duration of surgery. Differences for

Table 1. Demographic, Anesthesiological, and Temperature Data

Parameter	BairHugger (FA) forced-air warming	HotDog (RP) resistive polymer warming	
Age (y)	39 ± 16	37 ± 13	P = NS
Gender (male/female)	16/24	31/9	$P < 0.01$
Body mass index (BMI; kg/m^2)	25.5 ± 4.0	25.6 ± 3.4	P = NS
Anesthesia (general/regional/combined)	32/3/3	32/4/3	P = NS
Duration of surgery (min)	91 ± 41	83 ± 40	P = NS
Duration of anesthesia (min)	110 ± 43	95 ± 41	P = NS
Blood loss (mL)	54 ± 54	38 ± 44	P = NS
Sevoflurane (end-tidal vol%)	2.0 ± 0.7	1.9 ± 1.1	P = NS
Fentanyl ($\mu g \cdot kg^{-1} \cdot h^{-1}$)	1.6 ± 0.8	1.7 ± 0.7	P = NS
Infusion (mL)	1243 ± 500	1180 ± 469	P = NS
OR temperature start (°C)	19.5 ± 0.4	19.5 ± 0.5	P = NS
OR temperature end (°C)	19.4 ± 0.6	19.5 ± 0.5	P = NS
Environmental temperature (°C) at 1 m distance to warming device (after 30 min)	24.4 ± 5.2	22.6 ± 1.9	AUC: $P < 0.01$
Core temperature start (°C)	36.1 ± 0.5	36.0 ± 0.4	P = NS
Core temperature end (°C)	36.4 ± 0.5	36.2 ± 0.4	P = NS
Slope of core temperature curve (after 30 min to end °C per hour)	0.33 ± 0.34	0.29 ± 0.35	P = NS
Mean body temperature start (°C)	34.7 ± 0.6	34.8 ± 0.4	AUC: P = NS
Mean body temperature end (°C)	35.9 ± 0.5	36.4 ± 0.3	AUC: P = NS
Mean skin temperature start (°C)	32.2 ± 1.2	32.5 ± 0.9	AUC: P = NS
Mean skin temperature end (°C)	34.6 ± 1.3	35.8 ± 1.14	AUC: P = NS
Thermal comfort VAS (0–100)	51 ± 6	56 ± 11	P = NS

AUC = area under parameter curve (normalized for operation duration); VAS = visual analog scale; OR = operating room.

demographic and morphometric variables between the RP and FA groups were calculated with unpaired Student t test, distribution of gender was calculated with Fisher exact test, and distribution of anesthesia method with χ^2 test. Results are expressed as means ± SD. Differences were considered statistically significant at $P < 0.05$.

RESULTS

Eighty patients were assigned to either the FA (n = 40) or the RP group (n = 40) and treated as intended by protocol. There were no differences in demographic and morphometric characteristics (Table 1), except for gender with more female patients in the FA group.

After induction of anesthesia, core temperature decreased similarly for a period of approximately 30 minutes in both groups (Fig. 1). Subsequently, core temperature increased at comparable rates in both groups (0.33 °C/h ± 0.34°C/h and 0.29 °C/h ± 0.35°C/h for groups FA and RP, respectively; P = 0.6). There were also no differences between the 2 groups in the course of core temperature (Fig. 1, Table 1; P = 0.12), mean body temperature (Table 1; P = 0.11), and mean skin temperature (Fig. 2, Table 1; P = 0.48; all P values for comparison of normalized AUCs). We did not find significant intragroup core temperature differences between patients with esophageal and bladder core temperature probes (results not shown).

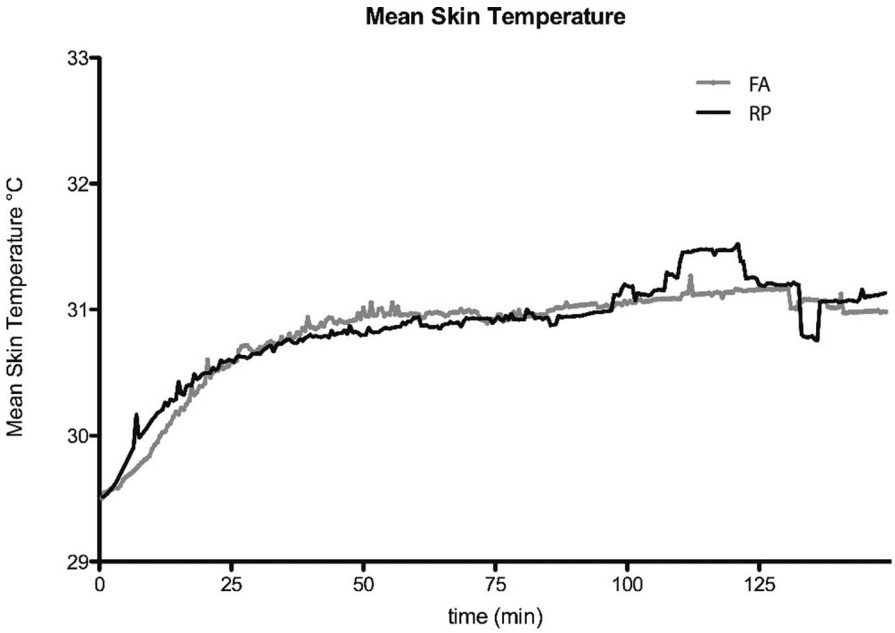

Figure 2. Mean skin temperature (0 minute represents induction of anesthesia). Gray: forced air (FA) (n = 40); black: resistive polymer (RP) (n = 40).

There were no differences in end-tidal sevoflurane concentrations or administered fentanyl between the 2 groups (Table 1). No patient in this study needed postoperative warming in the recovery room. Thirty minutes after admission to the postanesthesia recovery room, the patients' thermal comfort (evaluated using the VAS) was not different between the FA (VAS 51 ± 6) and RP (VAS 56 ± 11, $P = 0.09$) groups.

There were no heat-induced injuries or other device-associated complications in any of the patients. Maximal skin temperature was 39.2°C (chest) in 1 patient in the FA group and 39.3°C (abdomen) in 1 patient in the RP group. The room temperature and the environmental temperature (close proximity to the patient) were not different at induction of anesthesia between the FA and the RP groups. In contrast, the environmental temperature in close proximity to the workplace of the surgical and anesthesia team increased more with the FA patient warmer (24.4°C ± 5.2°C for FA vs 22.6°C ± 1.9°C for RP at 30 minutes, $P_{AUC} < 0.01$; Table 1).

DISCUSSION

Induction of anesthesia leads to a temperature redistribution from core to periphery, which is difficult to prevent with passive methods (e.g., insulation),[18,19] thus almost every patient is dependent on active warming to prevent accidental perioperative hypothermia. FA warming represents a quasi-standard for perioperative thermal management because of its high efficacy and safety.[6–9,20,21] Efficacy is defined by blower strength, air temperature, and the covered skin area.[21,22] However, blower strength is limited by fan noise and energy consumption, the covered skin surface is limited by the dimensions of the surgical field, and the air temperature is limited by the heat tolerance of the human skin. Thus, the highest allowed setting for air temperature on most heating devices is 43°C. The danger of thermal injury is highest in compressed, poorly perfused lower parts of the body; however, FA devices warm primarily the uncompressed, well-perfused upper parts. Consequently, FA warming has proved to be safe as long as it is applied correctly.[6–8] Some intrinsic limitations of FA warmers include the expense of using disposable blankets for each patient; the noise of the fan; and the increased OR temperature in the proximity of the device, resulting in thermal discomfort of the surgical staff. Other concerns include potential contamination of the parts of the FA device (e.g., hose and blower) with bacterial pathogens,[23] which could be transferred by the airstream to the surgical field and cause infections.[24] However, several studies challenged the clinical relevance of these results and found no differences in bacterial dispersion with or without FA.[25,26]

The new warming device (Hot Dog) uses a different technology: resistive warming of a polymer blanket. Potential advantages of resistive warming compared with FA warming include the following: all parts of the system are reusable, thereby reducing costs and the environmental burden; there are no moving parts, thus the system is very quiet; there is possibly less warming of the OR environment, resulting in increased thermal comfort for OR staff; and cleaning and disinfection are relatively easy, thus decreasing the risk of colonization with pathogens. There are, however, some disadvantages of the RP system. First, the blanket is stiffer and tends to wrinkle, which may reduce the surface area in contact with the patient's skin, thus reducing its effectiveness. Because there is no stream of warm air, the efficacy of the system, similar to all resistive-warming systems, is dependent on close skin contact, and the blanket has to be placed on the patient correctly. Incorrect placement may explain the observed tendency of the rewarming curve in the FA group to be steeper and the final mean core temperature in the RP group to be lower. Therefore, the results of our study should be extrapolated with care to settings in which the risk of severe intraoperative hypothermia is high, or those in which hypothermic patients must be warmed quickly from very low core temperatures. Another limitation is that the RP blanket has to be cleaned between cases, thus requiring manpower and cleaning equipment to avoid contamination with pathogens.

Our study demonstrates that intraoperative warming with the RP system was as effective as warming with the FA system. This is concordant to results in volunteers in which comparable heat transfer and core rewarming rates with RP and FA were found.[16] Several previous studies already showed that (carbon-fiber) resistive warming is as effective as FA warming. Negishi et al.[12] showed in a study of 24 patients undergoing major abdominal surgery that resistive warming with a carbon-fiber blanket was as effective as FA warming. More recently, Fanelli et al.[10] demonstrated comparable efficacy of a carbon-fiber resistive-warming blanket versus FA warming in 56 patients undergoing hip replacement.

In contrast, Russell and Freeman[14] found the resistive heating pad system inferior to FA warming with an underbody blanket in 60 patients undergoing liver transplantation. The limitation of this study was that different temperature settings were accepted (maximum for heating pad system was 39°C vs 48°C for FA warming). Leung et al.[15] studied 60 patients undergoing open abdominal surgery and compared a posterior resistive heating pad system with an FA warming system. They found significantly lower efficiency in the resistive heating pad group, with many patients remaining hypothermic at the end of surgery. Notwithstanding, as mentioned earlier, posterior patient-warming systems do have the inherent disadvantage that warming the back of the patient in the supine position is suboptimal because of low perfusion in this area and the danger of pressure-heat injuries.[27] In our study, the maximal skin temperature recorded with RP was 39.3°C compared with 39.2°C with FA. In the absence of ischemia or pressure, these values should be safe. This presumed safety is supported by the lack of heat-induced skin redness or injuries in any of our patients in either group.

There was also no difference in thermal comfort after anesthesia; active warming in the postoperative care unit because of hypothermia was not necessary in any patient in either group.

Interestingly, the OR temperature close to the patient increased significantly at 30 minutes, corresponding to the end of surgery in the first FA group patient. Although this may have resulted in decreased OR staff members' comfort, we did not measure their thermal comfort levels in this study.

This study has several limitations. Two different anatomic locations were used to measure core temperature (esophageal during general and combined general-regional anesthesia, and urinary bladder during regional anesthesia). These methods are both viable methods for core temperature measurements but are not completely interchangeable.[28] However, in this study, we found no significant temperature differences between regional anesthesia patients with bladder thermometry and general anesthesia patients with esophageal thermometry. Patients undergoing very long, open surgery with potential large fluid shifts are at highest risk for perioperative hypothermia. In our study, the mean duration of surgery was 90 minutes, and the typical surgery was limited to the extremities without open abdomen and without massive fluid shifts. This limitation of our study may reduce the applicability of our results to settings in which the risk of hypothermia is greater (prolonged open abdominal and trauma surgery).

In conclusion, RP warming was as effective as FA warming and may be considered an appropriate method for the prevention of accidental perioperative hypothermia.

STUDY FUNDING

Supported by the Research Fund of the Department of Anaesthesiology and Pain Therapy, Bern University Hospital, Inselspital, Bern, Switzerland. Thermocouples were donated by Mallinckrodt Anesthesiology Products, Inc., St. Louis, MO, and the Hot Dog system was donated by Augustine Biomedical Products, Eden Prairie, MN.

DISCLOSURE

Ruken Oguz's research fellow salary was partly paid by Augustine Biomedical Products, Eden Prairie, MN. The sponsors were not involved in data analysis or manuscript preparation.

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